Complete Summary

GUIDELINE TITLE

Temozolomide for the treatment of metastatic melanoma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Quirt I, Verma S, Petrella T, Bak K, Charette M, Melanoma Disease Site Group. Temozolomide for the treatment of metastatic melanoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Mar 20. 25 p. (Evidence-based series; no. 8-4). [38 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Unresectable metastatic malignant melanoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Dermatology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To evaluate the role of single-agent temozolomide in the treatment of patients with metastatic melanoma
- To evaluate whether the addition of interferon-alpha to temozolomide improves the disease-free survival, overall survival, or response rates compared to single-agent temozolomide
- To evaluate whether the addition of thalidomide to temozolomide improves the disease-free survival, overall survival, or response rates compared to single-agent temozolomide

TARGET POPULATION

Adult patients with unresectable metastatic malignant melanoma

INTERVENTIONS AND PRACTICES CONSIDERED

Single agent temozolomide

Considered but not recommended: interferon-alpha plus temozolomide, thalidomide plus temozolomide

MAJOR OUTCOMES CONSIDERED

- Response rate
- Disease-free survival
- Overall survival
- Quality of life
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Searches were performed in the MEDLINE (1966 to September week 3, 2005), EMBASE (1980 to 2005 week 40) and Cochrane Library (2005, Issue 3) databases. "Melanoma" (Medical Subject Heading [MeSH], Excerpta Medica Tree [EMTREE] term, and text word) was combined with "temozolomide" (EMTREE term and text word) or "temodal" (text word) or "temodar" (text word). These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and controlled trials.

In addition, the proceedings of the annual meeting of the American Society of Clinical Oncology (1997-2005) were searched for reports of newly completed trials. Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts meeting the following criteria:

1. Randomized controlled trials or meta-analyses of randomized controlled trials comparing single-agent temozolomide with another treatment for metastatic melanoma and reporting on response rates, disease-free survival, overall survival, quality of life, or adverse effects
2. Randomized phase II trials, single-arm phase II trials, or phase I trials investigating single-agent temozolomide, temozolomide combined with interferon-alpha, or temozolomide combined with thalidomide and reporting on any of the outcomes of interest
3. Evidence-based clinical practice guidelines and systematic reviews on the use of single-agent temozolomide in the treatment of metastatic melanoma

Exclusion Criteria

1. Trials published in a language other than English were excluded, due to limited translation resources.

NUMBER OF SOURCE DOCUMENTS

Two randomized phase III trials and three randomized phase II trials were located. In addition, phase II or I trials investigating single-agent temozolomide (n=9), temozolomide plus interferon-alpha (n=6) and temozolomide plus thalidomide (n=6), were reviewed. Sixteen of the trials were published as full reports, while ten were available only in abstract form.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Two randomized phase III trials were available for review and considered for pooling. Temozolomide was compared with dacarbazine in the first trial and a combination of temozolomide and interferon in the second. Pooling the data was judged inappropriate because the comparison arms were quite different.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This practice guideline report was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle. Evidence was selected and reviewed by two members of the PEBC Melanoma Disease Site Group (DSG) and by two methodologists.

The systematic review is a convenient and up-to-date source of the best available evidence on single-agent temozolomide or temozolomide in combination with interferon-alpha or thalidomide in the treatment of metastatic melanoma. The body of evidence in this review is primarily comprised of randomized controlled trials; therefore, recommendations by the DSG are offered. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada.

Disease Site Group Consensus Process

The recommendations were drafted by one member of the Melanoma DSG and circulated to the entire DSG in February 2004 for review and consensus. The Melanoma DSG unanimously agreed with the draft recommendations. Prior to the submission of the draft report to the Report Approval Panel (RAP), the DSG discussed adding a recommendation regarding the use of temozolomide for patients with brain metastases who require systemic treatment. After some debate, however, the members decided to address this issue as a qualifying statement.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

Following the review and discussion of Sections 1 and 2 of this Evidence-Based Series, the Melanoma Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Feedback was obtained through a mailed survey of 13 practitioners in Ontario (all participants were medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on April 23, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Melanoma DSG reviewed the results of the survey.

Report Approval Panel

The final Evidence-based Series report was reviewed and approved by the Program in Evidence-based Care (PEBC) Report Approval Panel in March, 2006. The Panel consists of two members, including an oncologist, with expertise in clinical and methodology issues.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- It is reasonable to use temozolomide at a dose of 200 mg/m2 orally for five days every four weeks as initial systemic treatment for patients with unresectable metastatic malignant melanoma.
- The addition of moderate-dose interferon-alpha 2b has produced a significantly higher response rate than single-agent temozolomide in a large randomized phase III study. However, overall survival was not altered and grade 3 and 4 hematologic toxicities were higher with the combined treatment. At the present time, the addition of interferon-alpha to temozolomide is not recommended.
- One randomized phase II study and six phase II studies have shown encouraging response rates when thalidomide is combined with temozolomide. However, dosing schedules of temozolomide in those studies differed from conventional prescribed doses and schedules. It is not clear

whether the improved response rates were due to the small number of patients in the studies, the different dose schedules of temozolomide, or the addition of thalidomide. Further phase III studies are required to confirm whether there is a benefit associated with the combination of temozolomide and thalidomide. Therefore, it is not recommended that thalidomide be combined with temozolomide at this time.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials and single-arm trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- One randomized controlled trial comparing temozolomide with intravenous dacarbazine was located. Response rates and overall survival were similar in the two groups. Progression-free survival was significantly prolonged with temozolomide (median 1.9 versus 1.5 months; p=0.012).
- A second randomized controlled trial compared temozolomide with temozolomide combined with interferon. Results from that trial indicate a significantly higher response rate with the combination treatment but no difference in overall survival. However, the difference in the time to the first formal disease assessment between arms may have influenced this difference.

POTENTIAL HARMS

See Table 2 in the original guideline document for grade 3/4 adverse effects found in studies of temozolomide.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Dacarbazine is the only chemotherapy drug currently approved for the treatment of patients with metastatic malignant melanoma, with response rates ranging from 6% to 15% observed in large randomized trials. Virtually all responses are partial, with median durations of response of only seven to eight months. Given these overall disappointing results, there is consensus among most physicians treating patients with metastatic malignant melanoma that it is appropriate to recommend more convenient treatments or experimental treatments to these patients.

- Due to oral dosing, temozolomide is a reasonable choice, particularly for patients who would have difficulty travelling to cancer centres for intravenous chemotherapy.
- Temozolomide has demonstrated an efficacy equal to that of dacarbazine in a randomized phase III trial. However, unlike dacarbazine, temozolomide is a convenient oral treatment that penetrates the blood-brain barrier and has shown activity against brain metastases. Although surgery is the preferred treatment modality for patients with solitary brain metastases from melanoma, temozolomide is the preferred chemotherapy for patients with brain metastases who require systemic treatment.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Mar 20

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Melanoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Melanoma Disease Site Group (DSG) disclosed information on potential conflicts of interest. No potential conflicts were declared.

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This is the current release of the guideline.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Temozolomide for the treatment of metastatic melanoma: a clinical practice guideline. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 Mar 20. Various p. (Practice guideline; no. 8-4). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 30, 2006. The updated information was verified by the guideline developer on July 7, 2006.

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DISCLAIMER

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